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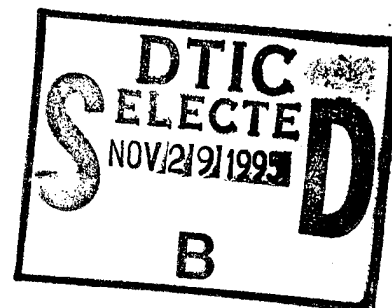
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INTRODUCTION

In a Mendelian trait, the genetic risk is the conditional probability that an individual has the genetic susceptible genotype given both phenotype and genotype information for all available pedigree members. Genetic risks may be based on the pedigree likelihood as originally proposed by Elston and Stewart (1971). In addition to such genotype risks, a phenotype risk may be defined as the conditional probability of developing the trait. With incomplete penetrance and absence of phenocopies, the phenotype risk is smaller than the corresponding genotype risk. Generally, however, phenocopies as well as genetic cases contribute to the phenotype risk.

The precision of risk estimates is dependent on the accuracy of the parameters used in their evaluation. Usually risks are computed under the assumption that genetic parameters are known without error. Uncertainty in the accuracy of parameter estimates renders uncertainty in the risk. Therefore, in order to evaluate the accuracy of a risk it is critical to calculate either a confidence or support interval for the risk (Weeks and Ott 1989; Ott, 1991).

Previously, we described a method to construct support intervals (SIs) for genetic risks working in a maximum likelihood framework (Leal and Ott 1994). Briefly, the method allows for parameters to vary in their support intervals. For each combination of parameter values so obtained, a risk is calculated whose associated log likelihood is equal to the log likelihood at the given parameter values. All those risk values with a log likelihood within m units of the maximum log likelihood form the risk support interval. Under this grant, as proposed, this method is expanded to allow for variability of genotype-specific penetrances when the age at disease onset is normally distributed. As an empirical example, the SIs for the phenotype and genotype risk have been calculated for a member of a breast-ovarian cancer kindred using two markers (D17S250 and D17S588) which are linked to the BRCA1 locus.

BODY

In genetic counseling situations, one generally works with a single pedigree. Usually, parameter estimates must be obtained from previously published results.

A maximum likelihood method to construct an SI for the risk under these circumstances was previously described (Leal and Ott 1994). In principle, we rely on published support intervals. If these are unavailable, we construct them by one of several methods using information in published reports.

As proposed under this grant, genotype-specific penetrance probabilities are incorporated in the calculation of SIs for the genotype and phenotype risk in the following manner: Approximate m -unit SIs are constructed around the mean age of disease onset, μ , and lifetime penetrances, λ , each for disease gene carriers and noncarriers. The calculation of maximum and joint log likelihoods for all parameters is carried out as previously described (Leal and Ott 1994), except that here, the estimates, μ , for age at disease onset are taken to follow a normal distribution while all other parameter estimates are binomially distributed. In the likelihood calculations, penetrance probabilities are the genotype-specific cumulative risk for unaffected and affected individuals when age of onset is unknown, and genotype-specific density for affected individuals when age of onset is known.

At this point, each parameter is varied within its SI. When the joint log likelihood for a set of parameter values falls within m units of maximum log likelihood, the genotype-specific penetrance probabilities are calculated for each liability class and the risk is calculated with the aid of MLINK (Lathrop and Lalouel 1984). The phenotype risk is also computed using a specific cumulative penetrance liability class. The highest and lowest (genotype and phenotype) risks so obtained are taken to be the endpoints of the (genotype and phenotype) risk SI. These changes have been implemented in the RISKSI program and described in a manuscript (Leal and Ott 1995).

As an empirical *example*, 2-unit SIs for the phenotype and genotype risk were calculated for individual 405, an unaffected 52 year old female who is a member of the breast-ovarian cancer kindred CRC101 (Smith et al. 1993), given her current age. Technical details may be found in the manuscript (Leal and Ott 1995). The resulting SI for the genotype risk that she carries the BRCA1 susceptibility allele ranges from 0 through 14.5%, and the SI for her phenotype risk is between 5.9% and 19.4%. The point estimates for the genotype and phenotype risk are 2.1% and 8.4%, respectively.

CONCLUSIONS

The calculation of support intervals enables genetic counselors to determine the reliability of risk estimates. An SI for the risk can help to determine the accuracy of the risk estimate, where a wide SI reflects an inaccurate point estimate.

REFERENCES

Elston RC, Stewart J (1971): A general model for the analysis of pedigree data. *Hum Hered* 21:523-542

Lathrop GM, Lalouel JM (1984): Easy calculations of lod scores and genetic risks on small computers. *Am J Hum Genet* 36:460-465

Leal SM, Ott J (1994): A likelihood approach to calculating risk support intervals. *Am J Hum Genet* 54:913-917

Leal SM, Ott J (1995) Variability of Genotype Specific Penetrance Probabilities in the Calculation of Risk Support Intervals. *Genet Epidemiol* (in press)

Ott J (1991) "Analysis of human genetic linkage." Baltimore: Johns Hopkins University Press

Smith SA, Easton DF, Ford D, Peto J, Anderson K, Averill M, Stratton M, Ponder M, Pye C, Ponder BJA (1993) Genetic heterogeneity and localization of a familial breast-ovarian cancer gene on chromosome 17q12-q21. *Am J Hum Genet* 52:767-776

Weeks DE, Ott J (1989) Risk calculations under heterogeneity. *Am J Hum Genet* 45:819-821

APPENDIX

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